## Human Naive Pluripotent Stem Cells Model X Chromosome Dampening and X Inactivation.

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**Public Summary:**
Naive human embryonic stem cells (hESCs) can be derived from primed hESCs or directly from blastocysts, but their X chromosome state has remained unresolved. Here, we show that the inactive X chromosome (Xi) of primed hESCs was reactivated in naive culture conditions. Like cells of the blastocyst, the resulting naive cells contained two active X chromosomes with XIST expression and chromosome-wide transcriptional dampening and initiated XIST-mediated X inactivation upon differentiation. Both establishment of and exit from the naive state (differentiation) happened via an XIST-negative XaXa intermediate. Together, these findings identify a cell culture system for functionally exploring the two X chromosome dosage compensation processes in early human development: X dampening and X inactivation. However, remaining differences between naive hESCs and embryonic cells related to mono-allelic XIST expression and non-random X inactivation highlight the need for further culture improvement. As the naive state resets Xi abnormalities seen in primed hESCs, it may provide cells better suited for downstream applications.

**Scientific Abstract:**
Naive human embryonic stem cells (hESCs) can be derived from primed hESCs or directly from blastocysts, but their X chromosome state has remained unresolved. Here, we show that the inactive X chromosome (Xi) of primed hESCs was reactivated in naive culture conditions. Like cells of the blastocyst, the resulting naive cells contained two active X chromosomes with XIST expression and chromosome-wide transcriptional dampening and initiated XIST-mediated X inactivation upon differentiation. Both establishment of and exit from the naive state (differentiation) happened via an XIST-negative XaXa intermediate. Together, these findings identify a cell culture system for functionally exploring the two X chromosome dosage compensation processes in early human development: X dampening and X inactivation. However, remaining differences between naive hESCs and embryonic cells related to mono-allelic XIST expression and non-random X inactivation highlight the need for further culture improvement. As the naive state resets Xi abnormalities seen in primed hESCs, it may provide cells better suited for downstream applications.